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Chapter

Alloimmunization and Role of HLA in Pregnancy

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Abstract

Alloimmunization also known as isoimmunization, during pregnancy is the production of IgG antibodies by the mother against the paternally inherited antigens (IPA) in the foetus/newborn. The alloimmunization during pregnancy leads to various alloimmune disorders, such as, haemolytic disease of the foetus and newborn (HDFN), neonatal alloimmune neutropenia (NAN) and foetal and neonatal alloimmune thrombocytopenia (FNAIT) due to the production of maternal alloantibodies against the red blood cell antigen, neutrophils and platelets cell antigens, respectively. Recent studies suggest that maternal anti-HLA class I alloantibodies may also be the cause of FNAIT in addition to antibodies against platelet antigens. On the contrary, studies have also suggested that HLA-C, a classical HLA class I molecule, and HLA-G, a nonclassical HLA molecule, play an important role in placentation and modulation of the maternal immune system during pregnancy, respectively, and thereby leading to acceptance of the semi allogeneic fetus. So far most of the studies have discussed alloimmunization in pregnancy relating to Rh antigen. Thus, in this chapter an attempt has been made to discuss alloimmunization in pregnancy caused because of maternal alloantibody against HLA antigen and its role in immune modulation during pregnancy.

Keywords: HLA, MHC, HLA-G, IPA

1. Introduction

Mammalian pregnancy with haemochorial placentation is an immunological contradiction with suppression of an immune response against the semi allogeneic foetus having inherited paternal antigens foreign to mother [1]. The foetus is not rejected as it would have, ideally in case of an unmatched organ transplant, wherein the immune system forbids the incursion of any genetic material or protein foreign to itself [2].

The protective mechanism which leads to acceptance of the semi allogeneic foetus includes: (i) Complete separation of maternal and foetal blood circulation. (ii) Low expression of foetal antigens that may stimulate graft rejection. The trophoblast cells originating from foetus lack expression of classical HLA class Ia and class II antigen except for very low expression of HLA-C antigens. They express HLA class Ib antigens which are known to modulate immune responses at the feto-maternal interface [3]. (iii) Involvement of both mother and foetus in order to

maintain pregnant uterus as an immune privileged site. (iv) Programming of the maternal immune response by factors obtained from placental and extra placental membrane [4].

Maternal and foetal cells interact in co-ordination to maintain an immune privileged environment at feto-maternal interface; some instances do occur which lead to maternal sensitization thereby leading to various disorders in the foetus/neonate. Alloimmunization during pregnancy is the stimulation of maternal immune response by the paternal inherited foetal or placental antigens [5].

The recognition of antigens as self and non-self is the essential process by which the immune system determines whether or not to develop an immune response. The response of the maternal immune system will depend on genetic and acquired factors related to the foetus and to antigen immunogenicity. Maternal alloimmunization occurs when the foetal and the maternal lymph combine due to rupture of placental barrier which often happens during delivery, although feto-maternal haemorrhage (FMH) may also result early in pregnancy. The instance of FMH has been observed in 7, 16, and 29% of mothers during their first, second and third trimesters, respectively [6]. Other maternal factors responsible for maternal sensitization involve factors such as Rh incompatibility, major surgical procedure, blood transfusion, multiparity, or operative removal of placenta [7].

The major antigens against which the maternal alloimmunization occurs are RBC, granulocytes (neutrophils), human platelet antigens and HLA antigens. The sensitization against these antigens leads to disorders, such as, haemolytic disease of foetus and newborn (HDFN), neonatal alloimmune neutropenia (NAN) and foetal and neonatal alloimmune thrombocytopenia (FNAIT), respectively.

Till now most of the studies have addressed the maternal alloimmunization relating to Rh and platelet antigen, this book chapter aims at exploring the role of human leukocyte antigen (HLA) in pregnancy and alloimmunization along with other factors.

2. Role of HLA in pregnancy

The human leukocyte antigen (HLA) also known as the major histocompatibility complex (MHC) play a very crucial role in enabling the immune system to differentiate between "self" and "non-self-antigen" [8]. It is situated on the short arm of human chromosome 6p21.3, and codes for nearly 130 structural genes known to function in antigen presentation to immune system thereby modulating the immune response. It is categorized into three classes i.e., class I, class II and class III [9]. The HLA class I gene is further classified into classical HLA class Ia genes (HLA-A, -B, -C) and non-classical HLA class Ib genes (HLA-E, -F, -G) [3]. The non-classical HLA class Ib genes show limited polymorphism as compared to those of classical HLA class Ia genes [10]. The HLA class II is differentiated into HLA-DR,-DQ,-DM and -DP.

The HLA class I molecules are known to interact with CD8+ T cells, natural killer cells (NK cells), and class II molecules with CD4+ T cells, respectively [11, 12] to elicit an immune response in order to eliminate the foreign or non-self-antigens. In contrast the non-classical HLA class Ib molecules interact with natural killer cells (NK cells) and other immune cell to develop an immunological tolerogenic effect. HLA plays a very important role in transplantation, as it is known to evoke an immune response to the transplanted graft, thus are very critical in pregnancy from gamete formation to completion of development, as foetus is the most successful semi-allograft.

The non-classical HLA class Ib molecules, primarily HLA-G plays a very important role in maintaining maternal tolerance i.e., an immunosuppressive state during pregnancy thereby contributing to foetal endurance and growth. Consequently inability in maintaining the maternal tolerance to the foetus, adversely affects the pregnancy leading to complications such as recurrent spontaneous abortion, foetal growth restriction, and preeclampsia [13]. Also HLA-C along with KIR (killer-immunoglobulin receptor) has been implicated to play a role in placentation. Thus, the role of HLA along with other immune cells may be implicated in maintaining pregnancy as well as at time in leading to pregnancy complications.

2.1 HLA-G in immune modulation during pregnancy

Among the non-classical HLA class Ib genes HLA-G is the most studied because of its role in immune modulation during pregnancy and its association with complexities like pre-eclampsia and recurrent spontaneous abortion in pregnancy [14].

2.1.1 Structure and expression of HLA-G

The non-classical class Ib HLA-G gene is situated near to the classical class Ia HLA-A gene on chromosome 6 and is also greatly homologous to it. The HLA-G gene comprises of seven intronic regions and eight exonic regions. The exon 1 codes for the signal peptide. The exons 2–4 code for the external part of HLA-G molecule which consist of three parts viz. α1, α2 and α3 domains, exon 5 encodes for the transmembrane region, where as exon 6 and a very short part of exon 8 encode for the cytoplasmic tail of the HLA-G molecule. The HLA-G gene is translated into a 38 kDa protein having similar structure as that of HLA class I antigens. It consists of a heavy chain that binds a light chain β2-microglobulin a protein coded by a gene on chromosome 15. The α1 and α2 extracellular domain of heavy chain form the peptide binding groove [15].

The HLA-G antigen has seven splice variants (HLA-G1-HLA-G7) as a result of alternative splicing event of the mRNA from the single HLA-G gene, of which HLA-G1 is the full length variant and the rest are formed by out-splicing of exons. Out of the seven isoform HLA-G1, HLA-G2, HLA- G3 and HLA-G4 are membrane-bound and the remaining three i.e., sHLA-G5, sHLA-G6 and sHLA-G7 are soluble isoforms [16]. The coding region of HLA-G gene shows meagre polymorphism but the polymorphisms that are present are equally shared by introns and exon 2, 3 and 4. Most of these polymorphism do not modify the protein sequence and those which do modify the protein sequence permit to be grouped in major allele groups like G*01::xx, G*01:02, G*01:03: xx, G*01:04: xx, G*01:05 N (null allele), G*01:06, and G*01:07 to G*01:18. Overall there are 61 alleles and 19 protein groups representing an amino acid substitution have been delineated in the HLA-G gene sequence [WHO Nomenclature Committee for factors of the HLA System and the International Immunogenetics Information System (IMGT)/HLA Database] [15].

HLA-G expression was first reported on human non-villous cytotrophoblast cells [17]. Its expression is stringently confined to certain cells, being largely expressed in extravillous cytotrophoblast cells. HLA-G5 a soluble variant is present throughout the placenta, within the chorion membrane, maternal blood and the decidua [18]. Apart from placental expression soluble HLA-G proteins are present in peripheral blood of pregnant women, non-pregnant women and men. The presence of sHLA-G in the blood of non-pregnant women indicates that it may play

an important role in reproduction even before conception. Soluble HLA-G is also found in follicular fluid, fertilized oocyte and in male reproductive tissue including semen [14]. HLA-G presence can also be detected in tissues like thymic medulla, cornea, pancreas and in human mononuclear phagocytic cells [53]. Its expression can be stimulated in condition following transplant, viral infections, autoimmune diseases and tumors [19].

2.1.2 HLA-G polymorphism

Both coding and non-coding regions of HLA-G gene display polymorphism. Exonic polymorphism may affect biological function such as binding of peptides or production of isoforms; whereas intronic polymorphism may influence the expression of the gene. Codon 31, 35, 57 and 69 of Exon 2 and codon 93, 107 and 110 of exon 3 coding region display majority of the polymorphism. A large number of SNPs (single nucleotide polymorphism) have been found in the non-coding region, including the promoter region at 5′UTR (untranslated region) and the 3′UTR. Some of these polymorphisms located near the regulatory element have an impact on the binding of the corresponding factors.

A 14 bp deletion/insertion have also been reported in the 3′UTR region of exon 8. These 14 bp del/ins are suspected to affect the size and stability of the mRNA transcripts. It was noticed by Rousseau et al. that a 14 bp insertion of sequence (5′-ATTTGTTCATGCCT-3′) lead to deletion of 92 bp sequence in the 3′UTR region, thereby resulting in production of more stable transcript. Few polymorphisms that may also effect the stability of mRNA transcripts, including the SNPs located at the position +3142 (C/G) and at +3172 position (G/A) in the 3′UTR region [19].

2.1.3 Immune modulation by HLA-G during pregnancy

Approximately 40% of the decidual tissue comprise of maternal immune cells at the beginning of pregnancy. Majority of these immune cells are natural killer (CD56 bright 16−) cells which are distinct from the NK cells (CD56 dim16+) present in the peripheral blood as the decidual NK cells have reduced cytotoxic activity. Also the decidual NK cells have a higher expression for genes encoding for integrins, lectin-like receptors, KIR (killer-immunoglobulin like receptors) and cytokines. Along with the presence of NK cell decidual tissue also show the presences of macrophages, T lymphocytes and dendritic cell [19, 20].

The trophoblast cells of the embryo express HLA-G antigen since the beginning of the first trimester and are present till the end of pregnancy. The interaction of HLA-G protein at the feto-maternal interface with the immune cell of the decidua ensures the foetal tolerance by inhibition of cytotoxic activity of NK cells and CD8+ T cells, suppressing the proliferation of alloreactive CD4+ T cells, suppressing the B cell activity, leading to the secretion of Th2 cytokines and stimulation of regulatory T cells (Treg) [19].

HLA-G intercedes its immunosuppressive activity by interaction of alpha 1 domain with inhibitory receptors expressed on immune cells. Leukocytes express inhibitory receptors like immunoglobulin-like transcripts (ILT)-2, ILT-4 and KIR. CD4+ and CD8+ T cells, B cells, monocytes, macrophages and myeloid dendritic cells (DC) display ILT-2, interact with only heterodimers of HLA-G1 or sHLA-G5 and ß2m. ILT-4 displayed by monocytes, macrophages and myeloid DC's have the capability to also interact with monomers of HLA-G whereas the NK cells interact through the KIR2DL4 expressed by them [19] (**Figure 1**). The interaction of these immune cells like decidual NK cells, CD4+ and CD8+ T cells which are

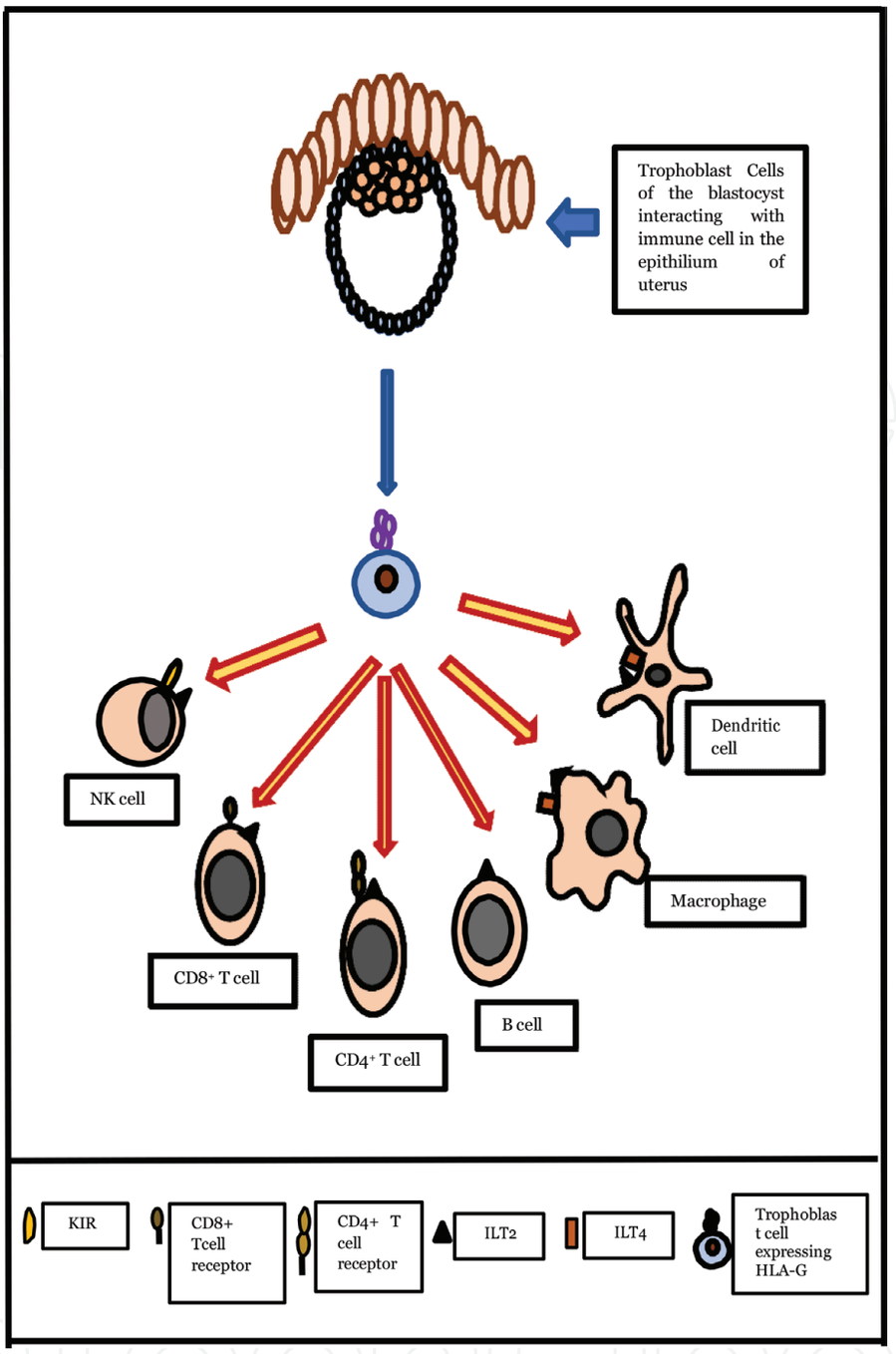

Figure 1.
HLA-G molecules expressed by the trophoblast cells interact with the inhibitory receptor KIR2DL4 expressed by the NK cells, ILT-2 (Ig-like transcript 2) expressed by NK cells, CD4+ and CD8+ T-cells and B-cells, and ILT-2 and ILT-4 expressed by macrophages and dendritic cells. The interaction of the HLA-G with its cognate receptors leads to immune tolerogenic effect thereby leading to the acceptance of the foetus by the maternal immune system.

HLA-G negative cells with trophoblast cell expressing HLA-G molecule leads to the acquisition of HLA-G molecule by immune cells thereby making them HLA-G+ cells through a process called as trogocytosis. Trogocytosis is a mechanism by which surface molecules may be transferred from one cell to another via cell to cell contact. The acquisition of the HLA-G molecule by these immune cells contributes to an immune suppressive milieu without them expressing HLA-G molecule, but only temporarily displaying it [21]. The acquiring of the HLA-G molecule by the decidual NK cells is preceded by a cycle of internalization, degradation and reacquisition of HLA-G. This cycle helps NK cells to maintain both tolerance and immune function [20].

2.1.4 HLA-G and pregnancy disorders

Abnormal placentation and immunological interaction at the feto-maternal interface are believed to play very crucial role in placenta-mediated complication of late pregnancy (viz. pre-eclampsia, foetal growth restriction, still birth and placental abruption) and foetal rejection in some pathological pregnancy, respectively. Deficient level of HLA-G expression and polymorphisms at HLA-G loci are known to be correlated to pregnancy complication especially pre-eclampsia and recurrent miscarriages (RM).

Pre-eclampsia is a pregnancy disorder which is clinically evident in the late second and third trimester of pregnancy [19]. It is characterised by high blood pressure, proteinuria and oedema associated with organ damage and prematurity. It is known to be a major cause of perinatal deaths, premature births and intrauterine growth restriction with an occurrence of 5–10% of all the pregnancy [22]. Though the major cause is unknown, various studies suggest that it may be related to maladapted immune system, with low levels of immune regulatory cell and low expression of HLA-G molecules [23]. The development of pregnancy has been strongly associated with level of soluble HLA-G molecules in the maternal blood. Maternal serum with higher levels of sHLA-G has been identified in females with successful pregnancy when compared with pre-eclampsia patients [24]. Lower sHLA-G levels in the maternal blood, with down regulated HLA-G and decreased proportion of HLA-G+ cells have been identified in patients with preeclampsia and are thought to be are strongly associated with preeclampsia [24–26]. The 14 bp ins/del in the 3′UTR of region exon 8 have been extensively studied, and it has been reported to be related to severe pre-eclampsia [15]. But on the contrary, there are studies which have reported no significant association of the 14 bp polymorphism with preeclampsia [24–26] implicating that differences in the ethnic population should be considered for the association between HLA-G 14 bp polymorphism and serum sHLA-G level. The SNP at position +3172 (G/A) leading to decreased in mRNA stability has been linked to pre-eclampsia [19]. Steinborn et al. reported that women with soluble HLA-G levels lower than 9.95 ng/ml have a risk of 7.1 for developing placental abruption during pregnancy as compared to healthy women [3].

Recurrent spontaneous abortion (RSA) is defined as the loss of two or more consecutive pregnancy with the same partner [27]. The major causes of RSA are considered to be chromosomal abnormalities, anatomical anomalies and endocrine disorders along with immunologic dysfunction [28]. Many studies have reported increased occurrence of HLA-G allele homozygous for 14 bp ins in women with RSA [19]. Also, a study has reported that decreased expression of HLA-G suppresses the function of decidual NK cells and thereby may lead to RSA [28]. SNPs−1573T>C and −1746C>A in the promoter region of HLA-G gene are shown to be associated with RSA [29]. As the level of sHLA-G is known to be associated with the pregnancy complication, the measurement of sHLA-G protein may be useful in primary diagnosis for the pathogenesis of pregnancy complications.

2.2 Role of HLA-C and KIR during pregnancy

Health of a foetus during pregnancy depends on the supply of nutrients and oxygen to the placenta. During placentation the foetal trophoblast cells infiltrate into the uterine wall, transforming the spiral artery (maternal artery supplying blood to the placenta) into a high-conductance vessel, thereby increasing the blood flow to about 100 folds [30]. This transformation allows adequate time for gas exchange and also provides sufficient nourishment to the foetus. Defective

infiltration of the trophoblast cells into the uterus leads to failure in arterial conversion, thereby leading the arterial blood to squirt into the intervillous space from the non-transformed arteries causing impairment of the villous tree (placentation). The impaired placentation leads to reduced transport of oxygen and starving of the foetus. The clinical manifestation of this failure may result in disorders such foetal growth restriction (FGR), preeclampsia, recurrent miscarriage (RM), unexplained still birth, placental abruption and preterm labour [31, 32].

The uterus shows abundance of decidual natural killer cells (NK cells) and thus, is thought to be involved in placentation and thereby in foetal development. Placenta is the site at which maternal allorecognition of the foetus takes place, wherein the foetal extra villous trophoblast cells (EVTs) encroach and unify with the maternal immune cells. Interaction of maternal KIR present on the uterine NK cells and its corresponding ligand, HLA-C which is the only classical HLA class I antigen expressed on the trophoblast cells of the foetus are claimed to regulate the process of placentation.

There are approximately 14 different KIR genes existing in a linear array in the leukocyte receptor complex (LRC) on chromosome 19q13.4. KIRs are differentiated on the basis of number of extracellular Ig-like domain (2 or 3) and cytoplasmic tail (long or short). They are known to regulate the activity of NK cells, either conferring them with an inhibitory or activating signal. Interaction of KIR with a long cytoplasmic tail (e.g., KIR2DL1) with its corresponding ligands leads to generation of an inhibitory signal, where as those having a short tail (e.g., KIR2DS1) results in activation of NK cells.

The activating and inhibitory genes are differentiated into two haplotype A and B. The KIR A haplotype is the most frequently occurring haplotype and consists of six inhibitory genes. The KIR B haplotype consist of gene which are more variable in their genetic content and are mostly activating KIR. Hence an individual's KIR genotype can be designated as "AA", "AB", and "BB".

The most important ligand for KIR is the HLA-C molecules, and there are approximately 4000 alleles of HLA-C. The HLA-C are differentiated into two distinct group by KIR, i.e., HLA-C1 and HLA-C2 [33]. HLA-C molecules with amino acid asparagine (Asn) at position 80 belong to HLA-C1 group, where as those with amino acid lysine (Lys) at the 80th position belong to group C2 of HLA-C. KIR2DL2/3 (inhibitory receptor) interacts with HLA-C1 allotype and KIR2DL1 and KIR2DS1 act as receptors for HLA-C present in C2 group [34].

Existence of KIR B haplotype in mother confers protection from pregnancy complications, where as its absence may increase the risk of complications [35]. The KIR B haplotype consist of activating KIR2DS1 receptor, which on interacting with its cognate ligand induces the NK cells to secrete granulocyte-macrophage colony stimulating factors and other chemokines known to promote placental trophoblast invasion. It also consists of KIR2DL1*004 which is the most common inhibitory KIR2DL1 allele on the B haplotype, and is known to have a weak interaction with HLA-C2 allotype as compared to alleles present on KIR A haplotype [36]. On the contrary, mothers homozygous for KIR A haplotypes (KIR "AA" genotype), with foetus having an additional C2 copy as compared to mother (i.e., mother C1/C2 with foetus C1/C2 or mother C1/C2 with foetus C2/C2), that to when the extra copy is of paternal origin are at an increased risk of having a complicated pregnancy [6]. As mothers with KIR AA haplotype have two copies of inherited inhibitory KIR for HLA-C2 allotype i.e., KIR2DL1, thus when the mothers uterine NK cells possessing KIR AA genotype interact with foetal trophoblast cells expressing HLA-C2 allotype, it induces a strong inhibitory effect on NK cell which is one of the reasons for defective placentation and in turn for various pregnancy related complications [37] (**Figure 2**).

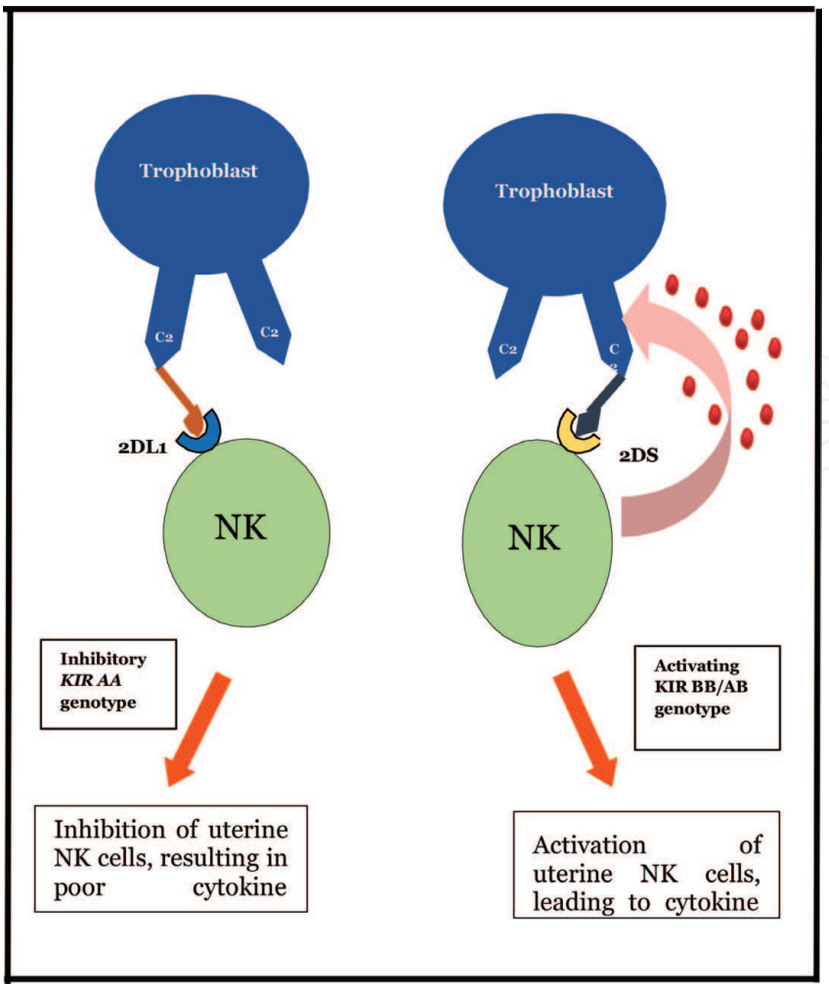

Figure 2.
Model for maternal KIR/foetal HLA-C interaction at the placentation site. The figure depicts foetus homozygous for HLA-C2 group with one paternally inherited HLA-C2 molecule. If the mother possesses KIR AA genotype, then the inhibitory KIR2DL1 receptor will interact with HLA-C2 molecule expressed by trophoblast cells leading to strong inhibition of uterine NK cells thereby resulting in defective placentation. On the contrary if the mother possess KIR AB or BB genotype, the activating KIR2DS1 receptor present in the KIR B haplotype interacts with HLA-C2 molecule expressed by trophoblast cells stimulating the of uterine NK to produce cytokines such as GM-CSF thereby resulting in normal placentation.

2.3 Clinical impact of H-Y alloimmunity in secondary recurrent miscarriages (SRM)

H-Y antigens are a class of minor histocompatibility antigens (mHAs), encoded on Y-chromosome are omnipresent in male cells including foetal and trophoblast cells. H-Y antigens exhibit a large amount of similarity to H-X antigen encoded on the X-chromosome, but they possess few distinct regions which make them highly immunogenic in nature. The H-Y alloimmunity has turned out to be, one of the potential reasons for SRM during pregnancy.

SRM is defined as three or more consecutive miscarriages following a successful pregnancy as compared to primary recurrent miscarriage (PRM), which is characterized by three or more miscarriages without a previous successful birth. PRM is supposed to be caused because of chromosomal defect along with improper implantation of the embryo, whereas SRM are more probably caused due to immunological responses [38].

Generally, during pregnancy the cellular and humoral anti-HY immune response is well tolerated by the foetus, but in minority of cases the H-Y alloimmune response may lead to complications during early or late pregnancy. It has

been implicated that pregnancy with a male foetus results in the development of alloimmune response towards the H-Y antigen by mother's immune system, thereby predisposing the mother to SRM and also impacting the prospect of subsequent pregnancy negatively in terms of perinatal complications and live birth [38, 39].

The presence of H-Y restricted HLA alleles along with H-Y antibodies, have also been related to the development of SRM and other pregnancy complications [38, 40]. The term "H-Y restricting HLA" is utilized to describe HLA alleles documented till date, which functionally exhibit H-Y peptides. H-Y restricting HLA alleles include the following HLA class I alleles: HLA-A*01, HLAA*02, HLA-B*07, HLA-B*08, HLA-B*52, HLA-B*60 and HLA class II alleles: HLA-DRB1*15, -DQB1*0501/2, -DRB3*03.

Possessing a HY restricting HLA class II alleles substantially decreases the prospect of live birth in patients with SRM and firstborn boys as compared to those with firstborn girl. It is implicated that the prospect of live birth decreases in a dose-response fashion with increasing number of maternal HY-restricting HLA class II alleles in patients with firstborn boys [40]. Maternal possession of HY restricting HLA class II alleles also reduces the long-term chance of live birth in females with SRM [41]. Whereas a mother homozygous for HLA-G 14 bps ins and carrying HY restricting class II alleles are predisposed to SRM with the first born boy and also negatively affect the birth weight of the boy [42].

In a study, antibodies against both HLA and H-Y antigens during early pregnancy were significantly higher in SRM females as compared to females with normal pregnancy. The prevalence of these antibodies were associated to low subsequent live birth rate whereas the existence of anti H-Y antibodies were related to low male/female ratio in subsequent live births [40]. The male: female ratio for SRM was observed to be 1.49 prior to miscarriages and 0.76 subsequent to miscarriages in a 20 years cohort study [38]. Thus, implicating H-Y antibodies in preventing implantation or successful gestation of male foetus. Considering H-Y antibodies as one of the factors responsible for SRM, IVIG (intravenous immunoglobulin) infusions are commonly used as treatment to neutralize the circulating antibodies, and it has been shown to improve the birth rates in patients with SRM [38].

3. Rh alloimmunization

The rhesus (Rh) blood group system comprises of more than 50 independent antigens and is highly polymorphic of the human blood group [43]. Following ABO, Rh blood grouping system is clinically important in transfusion medicine. The common Rh antigens are D, C or c, and E or e. Of which the D-antigen is greatly immunogenic and stimulates an immune response in 80% of person negative for D-antigen, when transfused with a D-antigen positive blood [44, 45]. Thus, D-antigen typing is routinely performed on every blood donor and transfusion recipient in order to avoid clinical complications due to mismatched transfusions. On the contrary, even with the use of anti-D immunoglobulin prophylaxis, there is still occurrence of D-alloimmunization in pregnancy.

D-alloimmunization (Rh alloimmunization) in pregnancy occurs due to incompatibility of D-antigen between the mother and the foetus. Generally, an individual is categorized as Rh-positive if they show an expression of Rh D-antigen on the erythrocytes, and Rh negative if there is no expression of D-antigen on the erythrocyte surface [46]. The Rh alloimmunization becomes clinically substantial when an Rh negative mother carries a foetus which is Rh-positive. The incompatibility of Rh antigen leads to sensitization of mother to the D-antigen, and also to the production of anti-D antibodies, which can adhere to and possibly lead to destruction of

Rh-positive erythrocytes of foetus. Nevertheless, the Rh incompatibility typically does not have an adverse consequence on the initial pregnancy as the foetus is delivered prior to the development of anti-D alloimmune response [47]. Although, it may also occur during the initial pregnancy due to spontaneous antenatal mixing of the foetal and maternal blood. In some instances such as miscarriage, abortion, trauma, childbirth and invasive prenatal diagnosis viz. chorionic villous sampling, amniocentesis, and pregnancy related uterine curettage may lead to feto-maternal haemorrhage thereby causing maternal exposure to foetal blood and consequently leading to alloimmunization [48]. The risk of Rh D immunization is estimated to be 1.5–2% in sensitized women following spontaneous miscarriage and 4–5% after dilation and curettage [49, 50]. Once the mother has been alloimmunized, subsequent pregnancies are at an increased risk, for the development of haemolytic disease of the new born (HDN) if the foetus is incompatible i.e., Rh-positive [45]. The diagnostic and clinical management of HDN is described in Section 4.1.

4. Disease caused due to alloimmunization in pregnancy

4.1 Haemolytic disease of foetus/newborn (HDFN)

Alloantibodies against the Rh antigen are the most common reason for intensive haemolytic disease in the neonates. Although the rate at which clinically significant HDFN occurs is relatively low viz. 3/100,000–80/100,000 live births [51]. In comparison to Rh antigen, alloantibodies to Kell (K and k), Duffy (Fya), Kidd (Jka and Jkb), and MNSs (M, N, S, and s) antigens, are also known to lead severe haemolytic disease in the foetus [52]. Although over 50 different non-ABO red cell surface antigens are thought to be involved in leading to HDFN, but the most relevant and significant alloantibodies causing HDFN are anti-RhD [44], anti-Rhc, and anti-Kell (K1) [53]. HDN due to Kell alloimmunization results in haemolysis and direct inhibition of erythropoiesis by Kell antibodies, as the Kell antigen is expressed on the surface of erythroid progenitor [6, 54]. Alloimmunization due to anti-Kell antibodies results in critical foetal disease even at lower maternal antibody titre than in Rhesus disease [6]. ABO incompatibility also causes HDN, but it occurs exclusively in mother with type-O blood with foetus having type-A or type-B blood. 1% of the type-O mothers possess a high titre of IgG antibodies against both A and B antigens. They cross the placental barrier and lead to haemolysis. Mothers with type-A or type-B antigen have the occurrence of IgM antibodies which are incapable of crossing the placental barrier thus have no role in alloimmunization during pregnancy [6].

A neonate delivered by an alloimmunized mother displays clinical indication based on the severity of the disease. General indications are jaundice, pallor, hepatosplenomegaly, and foetal hydrops in severe cases. Neonates with HDN very frequently suffer anaemia due to destruction of RBCs by reticuloendothelial system and in some due to intravascular destruction. Rarely conjugated hyperbilirubinemia is suffered by the neonate due to placental or hepatic dysfunction with severe haemolytic disease.

Foetal anaemia can be diagnosed using ultrasound, cardiotocography and cordocentesis [48]. High resolution ultrasonography has supported in early diagnosis of early hydrops and has also lowered the foetal trauma and fatality rate to approximately 2% while performing percutaneous umbilical blood sampling (PUBS) and placental trauma during amniocentesis. Rh and ABO alloimmunization can be diagnosed using indirect Coombs test and direct antibody test [6]. Currently in order to prevent alloimmunization in mothers having maternal and foetal Rh

incompatibility Rh immunoglobulin (RhIG) is administered at the 28th week of pregnancy. This has critically helped in reducing the instances of HDFN due to anti-D alloantibody [6, 55]. Postnatal HDFN treatment consists of intensive phototherapy and exchange transfusions to treat severe hyperbilirubinemia and top-up transfusions to treat early and late anaemia [56].

4.2 Foetal/neonatal alloimmune thrombocytopenia (FNAIT)

Maternal alloantibodies against foetal human platelet antigens (HPA) cause FNAIT. It is comparatively an infrequent condition occurring in 1–800/2000 live new born. The alloantibodies are IgG antibodies against the paternal HPA antigens and are responsible for destruction of platelets in the foetus or the newborn. Almost 80% of the instances of FNAIT are a consequence of maternal and foetal incompatibility to HPA-1a, the rest 20% results from incompatibility to HPA-5b on GPIa and other HPAs [57]. In addition to HPA antigens, antibodies against CD36 glycoprotein a member of class B scavenger receptor family [58] is also implicated in the causal of FNAIT. A case study reported, maternal deficiency in expression of CD36 protein lead to maternal immunization against CD36 protein (anti-NAK) [59]. The clinical impact of NAIT is related with maternal immunization against CD36 is analogous to that observed in infants affected by HPA specific antibodies [60].

Alloantibody production by maternal immune system requires the presentation of antigen to maternal T-cell through HLA class II molecules. It was reported that HPA-1a alloimmunization is mediated by interaction of HPA-1a peptides to HLA DRB3*01:01 molecule [57, 61]. This may be a consequence of feto-maternal haemorrhage, which can happen during delivery or abortion, as a consequence of platelet leakage into maternal circulation [62]. Maternal IgG alloantibody thus formed is progressively transported to the foetus through the neonatal Fc receptor, whereas the IgA and IgM are not transported as there are no specific receptors for them. Once through the placenta, the maternal alloantibody opsonises the foetal platelets thereby resulting in their destruction and leading to thrombocytopenia [62–64].

The clinical indication of FNAIT differs from asymptomatic thrombocytopenia to life threatening intracranial haemorrhage (ICH) [57]. Intraparenchymal haemorrhage in the temporal lobe is also most often noticed in FNAIT [65]. Studies have also shown that antibodies against HPA-1a antigen or thrombocytopenia may also result in decreased birth weight and a very low weight for gestational age which presents a health risk later in life [66]. In many of the FNAIT instance, the illness presents as, petechiae, hematomas, haemoptysis, retinal bleeding and haematuria [57, 67]. Occasionally, the bleeding due to FNAIT is diagnosed during foetal life in ultrasound abnormalities [68]. Without routine screening for HPA antibodies the disease is mostly detected after the delivery of the first affected child. Thus, making antenatal treatment and diagnosis possible only for subsequent pregnancies in order to prevent recurrence of severe FNAIT [69]. FNAIT may be diagnosed using antibody detection methods using serological or ELISA based techniques or by platelet typing using PCR-based assays.

The immediate treatment for thrombocytopenia in case of severe bleeding is platelet transfusion [68, 70]. In addition to transfusion intravenous immunoglobulin IVIG can be provided to prolong the survival of incompatible platelets and reduce the overall impact of thrombocytopenia [71, 72]. The most favourable antenatal treatment in order to prevent bleeding complications in pregnancies with FNAIT is non-invasive IVIG treatment on weekly basis [68]. In FNAIT resulting due to anti-CD36 glycoprotein intrauterine transfusions with compatible RBC and CD36 null platelets are useful in preventing the hazardous clinical effect of the disease [73].

4.3 Neonatal alloimmune neutropenia (NAN)

Neonatal alloimmune neutropenia (NAN) is a very rare disorder, but is a life threatening disorder of the neonates. The occurrence of NAN has been estimated to be 1 in 1000/6000 live births. NAN occurs due to maternal sensitization to incompatible paternal foetal granulocyte antigens. The maternal alloantibodies formed against the foetal granulocytes are transported through the placenta which thereby causes the destruction of foetal granulocytes [74].

Maternal alloantibodies against granulocyte-specific antigens HNA-1a and HNA-1b have been accounted widely to cause NAN. Antibodies to Fc gamma RIIb (CD16) and HNA-2a granulocyte antigen are infrequently involved in neonatal neutropenia, if mother is HNA-1 null phenotype [74, 75]. A case study has also reported the involvement of HNA-4b as a causative of severe NAN [76].

Neutropenia in neonates is a self-limiting disorder and lasts for only few weeks, but in some instances, it can prevail for as long as 6 months. In the course of this period, neonates are at severe risk of acquiring infection [75]. Symptomatic neonate suffering NAN frequently present with retarded umbilical cord separation, skin infections, otitis media, or pneumonia within 15 days of life. Most of the infections that occur are mild, but it may at times turn severe. The fatality rate because of NAN has been noted to be around 5%. The severity of NAN is dependent on concentration and the subclass of IgG present [74].

The immune neutropenia correlates with granulocytes specific antibodies present in the serum and can be diagnosed [75] using the granulocyte agglutination test (GAT), the granulocyte immunofluorescence test (GIFT), the monoclonal antibody immobilization of granulocyte antigens assay (MAIGA), an assay called as extracted granulocyte immunofluorescence assay (EGIFA) measures the anti-HNA-1a, -1b, and/or -2 antibodies in the sera. The use of EGIFA assay has been reported to improve the diagnosis and clinical management of patient suspected to have NAN [77]. The treatment for NAN is still a matter of discussion, but the options used for the management of NAN include antibiotics, intravenous immunoglobulin (IVIG), corticosteroids, and human granulocyte colony-stimulating factor (rhG-CSF) [78].

5. Conclusions

Table 1 summarizes the implication of HLA antigens in complications related to pregnancy. Though it is now well identified that the HLA plays major role in pregnancy, placentation and immune modulation to maintain an immune-tolerance

Disease/disorder	Associated HLA allele/ class	Study findings/outcomes	Reference
Rh isoimmunization	HLA A3, B17, CW2 and DR4.	Inheritance of HLA HLA A3, B17, Cw2 and DR4 increased the risk of Rh immunization.	Kumar et al. [79]
NAIT	HLA-DRB3*0101.	Presence of HLA-DRB3*0101 restricted CD4+ cells specific for HPA-1a antigen in alloimmunized women. Implicates strong association of DRB3*0101 in immunization of pregnant women against foetal HPA-1a antigen.	Ahlen et al. [61]

Disease/disorder	Associated HLA allele/ class	Study findings/outcomes	Reference
Reduced birth weight of foetus with NAIT	Maternal anti-HLA class I antibodies.	Increased level of maternal anti-HLA class I antibodies in thrombocytopenic neonates are associated with reduce foetal growth.	Dahl et al. [80]
Reproductive failure (recurrent miscarriages and pre-eclampsia)	Group 2 HLA-C alleles (C2).	Foetus expresses both maternally and paternally inherited HLA-C antigens. Substantial increase in the risk for reproductive disorders with mother possessing KIR "AA" genotype and foetus expressing more C2 copies than mother.	Hiby et al. [35]
Recurrent spontaneous abortion	HLA-G with 14 bp polymorphism and SNP 3127(C/G) in the 3′UTR.	Substantial increased frequencies of the genotypes with 14 bp polymorphism and the SNP3127 (C/G) in the 3′UTR in RSA women of Caucasian origin.	Larsen et al. [81]
Recurrent pregnancy loss (RPL)	−1573T > C and −1746C > A SNPs in the promoter of the HLA-G gene HLA-G promoter region haplotype H1(ATCCAGGTAC GCAA) H2(CTTCGAGAAC GCAG).	SNP −1573T > C and −1746C > A in the promoter region of HLA-G gene are associated with RPL H1 is associated with a decreased and H2 is associated with an increased risk of RPL.	Yazdani et al. [29]
Pre-eclampsia	HLA-G with 14 bp polymorphism.	Increased frequencies of the +14 insertion/deletion HLA-G genotype of offspring were associated with severe and early onset of pre-eclampsia in Chinese population.	Zhang et al. [82]
Secondary recurrent miscarriage	HY (male specific minor histocompatibility antigen).	Aberrant maternal immune response against foetal HY antigen play a role in secondary recurrent miscarriage and other pregnancy complications.	Christiansen et al. [40]
Still birth	HY-restricting HLA class II alleles.	Maternal carriage of HY-restricting HLA class II alleles decreases long-term chance of live birth in women with RPL after a boy.	Kolte et al. [41]

Table 1.
Role of HLA in pregnancy disease/disorders.

state. This in turn results in foetus being well accepted by the maternal immune system. Alloimmunization and other pregnancy complications result due to mal-adapted immune system when the maternal immune system is unable to maintain an immune tolerance state towards the foetus.

Conflict of interest

The authors declare no conflict of interest.

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